Traceable Therapeutic Strategy for Treatment of Breast Cancer with Mesenchymal Stem Cells (MSCs)

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With the ability of tropism towards tumors, mesenchymal stem cells (MSCs) have been considered to be attractive delivering vehicles for antitumor therapy. Molecular imaging allows noninvasive tracking of molecular or cellular processes in vivo, as well as evaluation of targeted cancer therapy. We recently exploited bioluminescence imaging (BLI) and near infrared (NIR) imaging to evaluate the interaction between human umbilical cord MSCs (hUC-MSCs) and pre-established tumor. Our results revealed that the transplanted hUC-MSCs played a critical antitumor role in vivo in a human breast cancer xenograft model by inhibiting tumor angiogenesis and inducing cell apoptosis. Our finding demonstrates that molecular imaging is a powerful tool in tracking cell delivery and tumor response to hUC-MSCs therapies as well as cellular and molecular processes in tumor, which will eventually benefit future preclinical studies in cancer diagnosis and therapy through accurate and sensitive imaging techniques.

Keywords: Mesenchymal stem cells (MSCs); Molecular imaging; Bioluminescence imaging (BLI); Near infrared (NIR) imaging; Cancer therapy


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Mesenchymal stem cells (MSCs) are multipotent stromal cells and bone marrow, adipose tissue as well as cord blood and placental tissues including umbilical cord, from where they are often isolated. With the ability to home into tumor sites, MSCs hold great promises for cancer therapy. Engineered MSCs with pro-drug activation enzymes, cytokines, apoptosis inducers or oncolytic viruses have been recently explored in a variety of preclinical models, revealing in selective tumor suppression with high efficient and overcoming the drug resistance to traditional chemotherapies. Despite the great therapeutic potential, several issues such as cell engraftment, and tumor response to MSCs therapies as well as cellular and molecular processes in tumor after MSCs administration, will continue to plague the arena of the usage of MSCs in cancer therapy. With the capabilities for visualization, characterization, and measurement of biological processes at the cellular and molecular levels in living, intact subjects, molecular imaging makes it possible for monitoring both the efficacy of MSCs therapy and the growth status of tumor simultaneously.
In our recent study, we developed a mouse model to analyze the behavior and efficiency of human umbilical cord-derived MSCs (hUC-MSCs) as a cellular vehicle for breast cancer therapy [2]. An in situ breast cancer model was developed with MDA-MB-231 cells carrying a reporter system encoding a double fusion (DF) reporter gene. Administration of ganciclovir (GCV), targeting of the HSV-ttk gene can achieve selective ablation of HSV-ttk expressing cells. The substrates for Fluc and Rluc are D-Luciferin and coelenterazine respectively. Dual BLI can be used for tracking tumor progression with Fluc and hUC-MSCs survival with Rluc simultaneously within the same animal.

We showed in this study that dual BLI can be used for tracking the hUC-MSCs dynamic distribution and tumor response to hUC-MSCs therapy within the same animal simultaneously. Using firefly and renilla luciferases imaging, we found that tumors were significantly inhibited by hUC-MSCs administration. Because the substrates for Fluc and Rluc are D-Luciferin and coelenterazine respectively, dual BLI can be used for tracking tumor progression with Fluc and hUC-MSCs survival with Rluc simultaneously within the same animal.

Series studies have revealed that MSCs can secrete various chemokines or cytokines, which may influence the tumor progression and metastasis other than innocent bystanders in the tumor microenvironment[2]. The potential roles of MSCs in cancer progression have been extensively studied.
explored and results demonstrated that MSCs may act as regulators of apoptosis, angiogenesis, and immune tolerance\(^1\). Relying on their origin and the type of tumor cells they interact with, MSCs may either promote tumor growth and metastasis or inhibit tumor growth by increasing cell death\(^1\). Our results revealed that hUC-MSCs engineered to express HSV-ttk reduced the growth of tumor in vivo and this effect was enhanced by ganciclovir (GCV) administration, but not achieve complete tumor regression. We showed that the introduction of a suicide gene into hUC-MSCs could produce a tumor-specific pro-drug converting cellular vehicle. Furthermore, our findings provide evidence that soluble factors secreted by hUC-MSCs can suppress angiogenesis and thereby inhibit tumor cells proliferation. This is consistent with other reports describing breast cancer inhibitory abilities of MSCs either from bone marrow or umbilical cord through PI3K/Akt and angiogenesis pathways\(^9\). The apparent paracrine findings we describe here may help to introduce a new dimension on the use of hUC-MSCs in cancer therapy.

In addition to monitoring the therapeutic effects in real time, molecular imaging also is ideally suited to measure biochemical and molecular processes in vivo related to tumor biology. Further by using near infrared (NIR) imaging, we reveal that hUC-MSCs could inhibit tumor growth to some extent through decreasing angiogenesis and inducing cell apoptosis. Angiogenesis is an essential step in tumor growth, metastasis \(^{10}\), which denotes vessel sprouting from pre-existing ones, controlled by a fine balance of pro- and anti-angiogenic molecules. In our study, NIR imaging serves as an effective parameter than measuring microvessel density (MVD) for determining targeted cancer therapy because it is noninvasive and can be used to assess living animals\(^{11, 12}\). Induction of cell apoptosis is the primary mechanism through which most cancer therapies lead tumor cell death. Early assessment of tumor response is required to better understand the numerous biochemical features after MSCs therapy. NIR imaging of Annexin V, an apoptosis probe, revealed that the cell apoptosis was promoted in hUC-MSCs treated group and this effect also can be enhanced by ganciclovir (GCV) application. Noninvasive imaging of tumor angiogenesis and apoptosis allows for monitoring therapeutic effects in real time, which will eventually lead to personalized molecular medicine\(^5\).

In this study, the dual bioluminescent imaging approach provides a versatile platform to visualize MSCs localization and tumor procession. Considering the specific tumor tropism and selective engraftment of MSCs, we can picture the use of engineered MSCs as a vector targeted to tumors as well as tumor microenvironments, which could benefit in the selection and monitoring of progression of the different treatment strategies. The findings in this study obtained through BLI may be transitioned to the clinic through combination with traditional techniques, such as positron emission tomography (PET) \(^{13}\) and magnetic resonance imaging (MRI) \(^{14}\), which have already been validated for visualization of transplanted MSCs. The applications of molecular imaging in cancer diagnosis and management, will hopefully lead to increase of patient survival rates.

To design desirable strategies and evaluate treatment responses or relapses, molecular imaging will play a significant role in MSCs mediated cancer therapy. For traditional experiments, labeled MSC can be monitored by immunohistochemical (IHC) staining \(^{15}\), or DNA polymerase chain reaction (PCR) \(^{16}\) to examine the migratory end point only after the animal has been sacrificed. Although sensitive, these kinds of methods need numerous animals to be sacrificed at multiple time points. To circumvent single time point experiments, in vivo non-invasive molecular imaging approach was employed to monitor the biodistribution of transplanted hUC-MSCs and therapeutic responses of pre-established tumor in this study. Beyond macroscopic imaging of tumor anatomy and perfusion, molecular imaging can be used to achieve the following: (i) detect, stage, and monitor cancer progression noninvasively, (ii) expedite cancer drug discovery \(^{17}\), and (iii) predict responders versus non-responders in the therapeutic course \(^{18}\) and help determine the overall effectiveness of therapies longitudinally\(^{19}\). Moreover, molecular imaging can help to unravel the underlying mechanisms of tumor growth and metastasis. Furthermore, BLI used in this study is an ideal and cost-effective technique for imaging small animals such as mice. By combining different luciferases/substrates, BLI provides a flexible and highly useful platform for cancer research\(^{5, 20, 21}\).

The ability of MSCs to migrate towards and engraft into the tumor sites, make them a promising targeted vehicles in cancer therapy. The real time in vivo imaging technologies provide accurate tracking of tumor progression or regression as well as therapeutic mechanisms of MSCs. This leads to the quest for innovative multifaceted solutions, such as improving treatment delivery, introducing novel anti-cancer molecules into MSCs and tracking of outcomes through sensitive and accurate molecular imaging methods in MSCs therapy for primary or metastatic tumors. It is expected to see more pharmaceuticals of engineered MSCs leading to beneficial anticaner effects to be used in clinic.

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Conflicting interests

The authors have declared that no competing interests exist.

References


